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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,690	12/05/2001	Philip Gerard Cavanaugh		4679
7590	08/24/2004		EXAMINER	
Philip G. Cavanaugh			HINES, JANA A	
26215 IVANHOE				
REDFORD, MI 48239			ART UNIT	PAPER NUMBER
			1645	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	10/002,690	CAVANAUGH, PHILIP GERARD
	Examiner Ja-Na Hines	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) Responsive to communication(s) filed on 24 May 2004.
- 2a) This action is FINAL.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) Claim(s) 36-49 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 36-49 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 05 March 2002 is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                    | Paper No(s)/Mail Date. _____.   |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|   | 6) <input type="checkbox"/> Other: _____.                                   |

**DETAILED ACTION**

***Election/Restrictions***

1. Applicant's election without traverse of claims 36-49 in the reply filed on May 24, 2004 is acknowledged.

***Priority***

2. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application 60/253,336 filed November 28, 2000 upon which priority is claimed fails because a claim for priority under 35 U.S.C. 119(e) cannot be based on said application, since United States application 10/002,690 was filed more than twelve months thereafter (December 5, 2001).

***Information Disclosure Statement***

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

4. The information disclosure statement should comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. Also, the filed information disclosure

statement requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed in order to comply with 37 CFR 1.98(a)(2).

### ***Drawings***

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following references not mentioned in the description: 4A-C, 6A-C, 7A-D and 8A-C. Corrected drawing sheets in compliance with 37 CFR 1.121(d), OR amendment to the specification to add the references in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The replacement sheets should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

***Specification***

6. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

7. The use of the trademarks with respect to reagent products has been noted throughout this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

***Claim Objections***

8. Claims 36-49 are objected to because of the following informalities: Claim 36 has periods at the end of each subsection, however the proper format is where there is one period at the end of the entire claim and the subsections can be setoff with semi-colons. Claims 45-46 have the same problem. Appropriate correction is required.

9. Claims 36 and 38 encompass the definition of a labeled ligand, a hapten and conjugated. This format is inappropriate, since definitions of words belong in the specification. Appropriate correction is required.

10. Claims 37-49 recite "The process as claimed in claim 36, wherein..." however suggested phrasing would be 'The process of claim 36, wherein...'.

11. Claim 37 recites "is-comprised" thus appropriate correction like making these two separate words is required.

12. Claim 38 comprises inappropriately capitalized "Wherein" clauses within the body of the claim. Claims 45-46, 48-49 have the same problem. Appropriate correction is required.

13. Claim 40 refers to "...a method comprised of, but is not limited to:" however this format is inappropriate. Appropriate correction is required.

14. Claim 42 recites "of of", Claim 46 recites "The The" thus appropriate correction is required.

15. Claims 43 and 44 are objected to because of the following informalities: The claims appear to be essentially duplicative and it is requested that applicant

either clarify the patentable difference between the claims or cancel one claim.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 38-39, 40 and 42-45 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

Independent claim 36 is drawn to a process for the evaluation of biological ligand binding and/or internalization using non-radioisotopic immunologically recognizable hapten-conjugated (labeled) ligands, consisting essentially of: an application step; a removal step, a solubilization step, an optional separation step; a blotting step; a detection step; and a optional determination step; dependant claims 38-39, 40 and 42-45, are drawn to any other antibody-recognizable entity (claim 38); any other protein, carbohydrate, nucleic acid, or any other substance or material which can possess said immunologically recognizable group (claim 39); other form of de-naturing or non-denaturing electrophoresis (claim 40); any other suitable blotting matrixes (claim 42); and other based detection (claim 43-45). The written description in this case only sets

forth specific antibody-recognizable entities; specific proteins or ligands; specific electrophoresis techniques; specific blotting matrixes; and specific detection techniques, therefore the written description is not commensurate in scope with the claims drawn to any other antibody-recognizable entity; any other protein, carbohydrate, nucleic acid, or any other substance or material which can possess said immunologically recognizable group; other form of de-naturing or non-denaturing electrophoresis; any other suitable blotting matrixes; and other based detection methods.

Neither the specification nor the claims teach how to define any other antibody-recognizable entity; any other protein, carbohydrate, nucleic acid, or any other substance or material which can possess said immunologically recognizable group; other form of de-naturing or non-denaturing electrophoresis; any other suitable blotting matrixes; and other detection methods. Neither the claims nor the specification teach how to obtain any other antibody-recognizable entity; any other protein, carbohydrate, nucleic acid, or any other substance or material which can possess said immunologically recognizable group; other form of de-naturing or non-denaturing electrophoresis; any other suitable blotting matrixes; and other detection techniques. There is no guidance as to what the any other antibody-recognizable entity; any other protein, carbohydrate, nucleic acid, or any other substance or material which can possess said immunologically recognizable group; other forms of de-naturing or non-denaturing electrophoresis are; or what other forms of de-naturing or non-denaturing electrophoresis; any other suitable blotting matrixes; and other forms of detection that can or cannot be used in the process being claimed. The specification does not include structural examples of any other antibody-recognizable entity; any other protein, carbohydrate, nucleic acid, or any other substance or material which can

possess said immunologically recognizable group; other forms of de-naturing or non-denaturing electrophoresis; any other suitable blotting matrixes; and other detection methods. Thus, the resulting any other antibody-recognizable entity; any other protein, carbohydrate, nucleic acid, or any other substance or material which can possess said immunologically recognizable group; other form of de-naturing or non-denaturing electrophoresis; any other suitable blotting; and other based detection could result in complexes used in the process not taught and enabled by the specification. Moreover, the claims are encompassing each and every type of antibody-recognizable entity, protein, carbohydrate, nucleic acid, or substance or material which can possess said immunologically recognizable group; other form of de-naturing or non-denaturing electrophoresis, yet the specification fails to disclose each and every type of antibody-recognizable entity, protein, carbohydrate, nucleic acid, or substance or material which can possess said immunologically recognizable group; other form of de-naturing or non-denaturing electrophoresis. The claims even encompass complexes not yet known, complexes which may later in time be classified as an antibody-recognizable entity; protein, carbohydrate, nucleic acid, substance or material; other forms of de-naturing or non-denaturing electrophoresis; other suitable blotting matrixes; and other detection methods, yet the specification fails to disclose such.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the *invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of specifically named antibody-recognizable entities; specific proteins or ligands; specific electrophoresis techniques; specific blotting matrixes; and specific detection techniques, the skilled artisan cannot envision the detailed structure of such, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. An adequate description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it.

Furthermore, *In The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of by only their functional activity does not provide an adequate description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus. Therefore the full breadth of the claims fail to meet the written description provision of 35 USC 112, first paragraph.

17. Claims 36-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preamble of the claim 36 is drawn to a process for the evaluation of biological ligand binding and/or internalization, however the recited steps within the process comprise an application step; a removal step, a solubilization step, an optional separation step; a blotting step; a detection step; and a optional determination step. There is no step which correlates the evaluation of biological ligand binding and internalization. Therefore, the goal of the preamble is not commensurate with the steps for the evaluation of biological ligand binding and/or internalization method that are drawn to identifying compounds.

18. Regarding claims 37-47, the phrase "but is not limited to" renders the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Moreover, it is unclear what limitations applicant is attempting to claim. The phrase appears to claim limitations not currently known in the art, thereby making the claims indefinite. Thus the metes and bound of the claims cannot be ascertained, thus the claims are indefinite and appropriate clarification and/or correction is required to overcome the rejection.

19. Regarding claims 38-40, 42, 44, and 46, phrases like "any other" or "other forms" renders the claims indefinite because the claims include elements not actually disclosed (those encompassed by "any other" or "other forms"), thereby rendering the scope of the claims unascertainable. See MPEP § 2173.05(d).

20. Claims 38-41 and 42 recite alternative limitations which are improperly expressed. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group recites members as being "selected from the group consisting of A, B and C". Another acceptable form recites "selected from 1, 2, 3, or 4." Applicant may correct this by amending the claim to recite the appropriate language.

21. The term "any other suitable blotting matrix" in claim 42 is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the specification nor claim define what makes a material suitable, thus the metes and bounds of the term are indefinite. Thus, appropriate correction is required to overcome the rejection.

22. Claims 43-44 refer to "other based detection", term is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term appears to claim limitations not currently known in the art, thereby making the claims indefinite. Thus the metes and bound of the claims

cannot be ascertained, thus the claims are indefinite since the claims fail to specifically recite the limitation. Appropriate correction is required to overcome the rejection.

23. Claims 44 recite the limitation "the avidin's or streptavidin's" in the claim. There is insufficient antecedent basis for this limitation in claim 36.

24. Regarding claim 45, the phrases "such as" or "etc" render the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

25. Claims 46-47 recite the limitation "the final antibody's" and "the avidin's or streptavidin's" in the claims. There is insufficient antecedent basis for this limitation in claims 36 or 44.

26. The term "varied conditions" in claim is a relative term which renders the claim indefinite. The term "varied conditions" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bound of the term is indefinite and it is unclear how the conditions are varied or variables can or cannot be changed. Therefore, appropriate correction is required by applicant to overcome the rejection.

27. Claims 48-49 recite the limitation "the same" in the claims. There is insufficient antecedent basis for this limitation in the claim. Claim 48-49 are indefinite in the recitation of "...followed by the same...". It is unclear what "same" applicant is referring to. Furthermore, the claim language is confusing since the claims are already dependant upon claims 36 or 37 and thereby incorporate the process recited by claims 36 or 37, thus it is unclear what same removing, separating, membrane binding and detection methods applicant is referring to. Correction is required to overcome the rejection.

28. Claims 36-49 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: There is no correlation step which recites how to evaluate a biological ligand to determine binding and internalization. Therefore the steps are incomplete and appropriate correction is required to overcome the rejection.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. Claims 36-49 are rejected under 35 U.S.C. 102(b) as being anticipated by

Cavanaugh et al., (1998).

The claims are drawn to a process for the evaluation of biological ligand binding and/or internalization using non-radioisotopic immunologically recognizable hapten-conjugated (labeled) ligands, consisting essentially of: an application step; a removal step, a solubilization step, an optional separation step; a blotting step; a detection step; and a optional determination step.

Cavanaugh et al., teach that transferrin, which is a biological ligand, binds to a specific cell surface receptor which binds two iron-saturated transferrin molecules and is responsible for the delivery of iron into cells either through internalization of iron-transferrin or activation of a plasma membrane that mediates the trans-plasma membrane transport of iron from transferrin (pages 48-49). The Materials and Methods teach a process for the evaluation of biological ligands binding and/or internalization using non-radioisotopic immunologically recognizable hapten-conjugated ligands. It is noted that conjugated biological ligands such as rat holo-transferrin can be purchased from commercial vendors (page 49). It is also noted that fluorescein-conjugated iron saturated (holo) human transferrin can be obtained from commercial sources. For the immunofluorescent detection of the cell surface transferrin, cells were grown on slides and primary antibody, anti-rat-Transferrin Receptor (TfR), or normal mouse IgG was added to the cells (page 49). Fluorescent-activated cell sorting (FACS) analysis was also performed wherein the cells were removed from culture plates; washed; and either normal mouse IgG or anti-rat-TfR was

added to the cell and the cells were analyzed for fluorescence using a FACSscan instrument (page 50).

Affinity isolation of TfR using immobilized transferrin was taught (page 50). The transferrin was immobilized on cyanogens bromide activated agarose gel which was later washed (page 50). To reduce inherent bound transferrin, cells were incubated before analysis (page 50). The cells washed and then lysed in dishes (page 50). The lysate supernatant was combined an excess of transferrin agarose and incubated. It is noted that the lysing steps are equivalent to the claimed solubilization steps. The gel was later harvested, washed and the bound-cell-lysate proteins were released by exposure of the gel to nonreducing sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) sample treatment (page 50). The sample was separated on a SDS-PAGE gel (page 50). This is equivalent to the claimed optional separation step comprised of electrophoreses and SDS-PAGE steps. Next the sample was blotted onto commercially available IMMOBILON membrane<sup>TM</sup> which is comprised of polyvinylidenediflouride(PVDF) (page 50). The membrane was incubated with a commercially available blocking solution containing streptavidin-horseradish peroxidase (HRP) (page 50). This teaches the instantly claimed blotting step. Then the membrane was washed and the HRP-enhanced chemiluminescence (ECL) substrate which is commercially available was applied and the light-emitting bands were detected and quantitated (page 50). Thus the detection of the blot-matrix associated labeled ligand was followed by luminescent techniques as required by the instant claims.

An additional procedure based on the affinity isolation of the TfR after biotinylation was used to quantitate cell-surface TfR in the cell lines (page 51). The cell surfaces were biotinylated, lysed and the resulting solubilized cell material was exposed to the immobilized transferrin (page 51). The agarose-transferrin preferentially bound to biotin-TfR in the lysate which was released with SDS-PAGE separation followed by electrotransfer and detection of biotinylated bands by incubation of the Western blot with streptavidin-HRP followed by ECL (page 51 and figure 5). Thus Cavanaugh et al., teach conjugated immunologically recognized groups, the same blotting methods, followed by luminescent methods or other detection methods based on streptavidin enzymes or traceable entities as instantly claimed.

Since the Patent Office does not have the facilities for examining and comparing applicants' process with the process of the prior art reference, the burden is upon the applicants to show an unobvious distinction between the material structural and functional characteristics of the claimed process of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Therefore, Cavanaugh et al., teach a process for the evaluation of biological ligand binding and/or internalization using non-radioisotopic immunologically recognizable hapten-conjugated (labeled) ligands, consisting essentially of: an application step; a removal step, a solubilization step, an optional separation step; a blotting step; a detection step; and a optional

determination step using the same steps and the same commercially available reagents with their well known properties as instantly claimed.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursdays and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*[Signature]*

Ja-Na Hines  
August 10, 2004

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